Remarks

Reconsideration and withdrawal of the rejections set forth in the Office Action dated November 5, 2003 are respectfully requested.

I. Amendments

Claim 1 is amended to clarify the method of preparation. Specifically, the claim is amended to describe the step of "preparing from a supersaturated solution of the compound liposomes at selected size intervals." Basis is found on page 8, lines 2-12, with specific reference to lines 6-7 which recite "...preparing several liposome compositions having different sizes...".

Claim 1 is also amended to include a step of "analyzing said liposomes for the presence of absence of precipitated compound", as set forth in pending claim 4 and on page 8, lines 7-8.

Claim 1 is also amended to clarify that "based on said analyzing, selecting liposomes of a size that corresponds to liposomes having no entrapped precipitated compound." Basis is found on page 8, lines 11-12.

Claims 4 and 5 are amended for consistency with claim 1.

Claim 9 is amended for clarification.

Claim 16 is amended to include similar langage discussed above with respect to claim 1.

Accordingly, no new matter is added by these amendments.

II. Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 3-9, and 16 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. These rejections are respectfully traversed.

1. Rejection of Claims 1 and 16: The Examiner maintains that since a specific method of preparation of liposomes is being claimed, the individual steps should be recited. Specifically, the Exaimenr assets that recitation of how the supersaturated

solution of the compound is entrapped in liposomes, how the size of the liposomes does not cause precipitation, and how the size is selected should be set forth.

Claim 1 is amended to recite these steps: (1) selecting a compound; (2) preparing lipsomes at selected size intervals from a supersaturated solution of the compound; (3) analyzing the liposomes for the presence of precipitated compound; and (4) selecting liposomes that have no entrapped precipitated compound.

Applicants have made a good faith attempt to amend the claims in such a way to address the points raised by the Examiner. If the Examiner remains dissatisfied, Applicants would appreciate some suggestions of claim language that would address the Examiner's concerns.

2. Rejection of Claim 9: The Examiner objected to claim 9 as unclear. The Examiner notes that the parent claim (claim 1) lists solvent pH as a condition that can maintain the compound above the room temperature solubility and that is is "unclear as to how the change of pH would change the temperature".

Claim 9 recites that "removing from an external liposome suspension medium the condition selected to maintin the compound above the room temperature solubility. Removal of the condition does not change the temperature, as the Examiner apparently understood, but returns the solubility of the compound to the room temperature solubility due to the removal of the condition, e.g, pH, that increased the compound's room temperature solubility.

Applicants reiterate that a good faith attempt is being made to bring the claims to a degree of clarity acceptable to the Examiner. If the Examiner remains dissatisfied, a specific suggstion of acceptable claim language would be appreciated.

In view of these comments and amendments, Applicants respectfully request that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

III. Rejections under 35 U.S.C. §102

Claims 1, 3-6, 8, and 16 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Mezel (EP Patent No. 0 177 223).

Claims 1, 3-6, 8-9, and 16 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Yamamoto *et al.* (EP Patent No. 0 551 169).

Claims 1, 3-9, and 16 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Abra *et al.* (PCT Publication No. WO 98/07409).

These rejections are respectfully traversed.

A. The Present Invention

The present invention describes a method for preparing liposomes having an entrapped compound in the form of a supersaturated solution. The method comprises **(i)** selecting a compound having a room temperature water solubility capable of at least a two-fold increase when an aqueous solution of the compound is treated by a condition selected from the group consisting of (a) increasing temperature, (b) adding a co-solvent, and (c) changing pH; **(ii)** preparing liposomes at selected size intervals from a supersaturated solution of the compound; **(iii)** analyzing the liposomes for the presence (or absence) of precipitated compound; and **(iv)** selecting liposomes of a size that has no entrapped precipitated compound.

B. The Cited Art

MEZEL describes preparation of a "multi-component" system (page 7, lines 6-9), where an active agent is present in "two" states, *i.e.*, in solution and in solid form within and outside lipid vesicles (page 7, lines 9-11). The active agent is dispersed in the product in (a) liposome encapsulated form; (b) in super-saturated solution form; and (c) in solid form.

YAMAMOTO ET AL. describe preparation of a liposome composition by warming an aqueous drug solution and mixing the warmed solution with a lipid solution to form liposomes (Col. 4, lines 25-34). The solution is then cooled to "ordinary" temperature (Col. 4, lines 19-21) to recover unencapsulated drug.

ABRA ET AL. describe a liposomal composition containing an entrapped cisplatin compound (page 1, lines 6-7). To prepare the liposomes, an aqueous cisplatin solution is heated to a temperature sufficient to achieve a two-fold increase in cisplatin solubility over its room temperature solubility (page 3, lines 12-14).

C. Analysis

1. Legal Standard

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131.

2. Analysis of Rejection over Mezel

Claims 1 and 16 of the present invention are directed to a method of preparing a liposome composition. The method includes the steps of **(ii)** preparing from a supersaturated solution of the compound liposomes at selected size intervals; **(iii)** analyzing said liposomes for the presence of absence of precipitated compound; and **(iv)** based on said analyzing, selecting liposomes of a size that corresponds to liposomes having no entrapped preceipitated compound.

Nowhere does Mezel teach these claim steps **(ii)**, **(iii)**, and **(iv)**. The method of liposome preparation in Mezel does not involve preparing liposomes at selected size intervals, analyzing the liposomes for the presence of precipitated compound, and based on the analyzing selecting a liposome size that corresponds to liposomes having no entrapped precipitated compound. In Mezel, liposomes of a single size are prepared and analyzed for the presence of absence of drug crystals (see, for example, Examples 1-7). Mezel does not teach preparing liposomes at selected size intervals and then selecting liposomes of a size that have no precipitated compound.

Accordingly, since Mezel fails to teach every element of the invention as claims, withdrawal of the rejection is respectfully requested.

3. Analysis of Rejection over Yamamoto *et al.*

Yamamoto *et al.* do not teach the steps of preparing liposomes at selected size intervals, analyzing the liposomes as a function of size for the presence of precipitated

compound, and based on the analyzing selecting a liposome size that corresponds to liposomes having no precipitated compound. Like Mezel, Yamamoto *et al.* report that the drug entrapped in liposomes prepared in accord with method described in Yamamoto *et al.* is in the "supersatured state or in the form of solid or crystals" (page 2, lines 21-23; emphasis added). Yamamoto *et al.* nowhere teach a step of selecting a liposome size that corresponds to liposomes having no precipitated compound.

4. Analysis of Rejection over Abra *et al.*

Abra *et al.* also fail to teach a step of selecting a liposome size that corresponds to liposomes having no precipitated compound. Nor does Abra *et al.* teach steps of preparing liposomes at selected size intervals and analyzing the liposomes as a function of size for the presence or absence of precipitated compound,

Accordingly, Applicants submit that standard of strict identity to maintain a rejection under 35 U.S.C. § 102 has not been met. Withdrawal of the rejections under 35 U.S.C. §102(b) is respectfully requested.

IV. Rejections under 35 U.S.C. §103

Claims 7 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over either of Mezel or Yamamoto *et al.* in combination with Woodle *et al.* (US Patent No. 5,013,556). This rejection is respectfully traversed.

A. The Invention

The present invention is described above. Dependent claim 7 includes the additional feature that the lipids for preparation of the liposomes comprise a lipid derivatized with a hydrophilic polymer.

B. The Cited Art

MEZEL is described above.

YAMAMOTO ET AL. is described above.

WOODLE ET AL. describe a liposome composition which contains between 1-20 mole percent of an amphipathic lipid derivatized with a polyalkylether, such as polyethyleneglycol.

C. Analysis

According to M.P.E.P. §2142, one of the three requirements to establish a case of *prima facie* obviousness, is that the prior art references teach or suggest all the limitations of the claim.

Claim 1, from which claim 7 indirectly depends, includes the steps of **(ii)** preparing from a supersaturated solution of the compound liposomes at selected size intervals; **(iii)** analyzing said liposomes for the presence of absence of precipitated compound; and **(iv)** based on said analyzing, selecting liposomes of a size that corresponds to liposomes having no preceipitated compound.

As discussed above, neither Mezel nor Yamamoto *et al.* show or suggest a method of preparation that involves these steps.

Woodle *et al.* is cited merely for the inclusion of lipids derivated with a hydrophilic polymer, and thus provide no teaching of the claimed steps. Thus, the combined teachings of Mezel and Woodle *et al.* or Yamamoto *et al.* and Woodle *et al.* do not show or suggest every feature claimed. Accordingly, dependent claims 7 patentably defines over the teachings of Mezel or Yamamoto *et* al. in combination with Woodle *et al.* Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

V. Conclusion

In view of the foregoing, Applicants submits that the claims pending in the application are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4310.

Respectfully submitted,

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